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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/803,702	MAINO ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-24,26-33, 35-55 and 61-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24,26-33, 35-55 and 61-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 19-24, 26-33, 35-55, 61-63, and newly added Claims 64-66 are under examination.

2. Applicant's amendments and remarks, filed 2/17/04 are acknowledged. As noted by Applicant, Claim 39 was improperly rejected under the first paragraph of 35 U.S.C. § 112 for lack of adequate written description.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 19-24, 26-33, 35-36, 40-55, and 61-63 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record. As set forth in the paper mailed 1/30/01:

"There is insufficient written description to show that Applicant was in possession of "an inhibitor of cytokine secretion" (Claim 19), other than Brefeldin A (BFA). The specification discloses no definition for said inhibitor and teaches only the single species, BFA. Absent any definition, the claim must be read broadly to include any chemical that could inhibit cytokine secretion, presumably including toxins ranging from benzene to sodium azide. Thus, the specification fails to adequately define the claimed invention and one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398."

Applicant's arguments, filed 2/17/04, have been fully considered but they are not persuasive. Applicant argues, "The description need only describe in detail that which is new or not conventional ... The rejection improperly requires Applicants to describe in detail an element which is neither new nor not conventional. The present claims are drawn to novel methods for detecting antigen-specific T cells by detecting intracellular cytokines following stimulation by contact with a nominal antigen. An inhibitor of cytokine secretion is used to allow intracellular cytokines to accumulate, thereby facilitating the detection of the intracellular cytokines."

It appears that Applicant is arguing that certain parts/aspects of the invention are new while other parts are not. In fact, none of the individual pieces of the claimed method are actually new, i.e., the activation of antigen-specific T cells is not new and neither is the detection of intracellular cytokines. What is new is the *combination* of techniques and steps that achieve a highly unexpected result, i.e., the detection of cytokines that were thought to exist at levels below the threshold of detectability. Accordingly, each aspect of the new and unexpected method must be adequately described for the claims to meet the written description requirement. In particular, it is the "inhibitor of cytokine secretion" that allows the intracellular cytokines to accumulate to a detectable degree. Accordingly, it remains the Examiner's position that an adequate written description of critical element is required.

Further note that Applicant has failed to address the Examiner's points regarding whether or not chemicals such as azide, chloroquine, cytochalasin, bafilomycin, or vincristine would be considered to be inhibitors of cytokine secretion in the claimed method. This line of reasoning can be carried a step farther - would the claims encompass the use of an anti-sense nucleic acid that could inhibit cytokine secretion (by blocking the expression of proteins involved in secretion)? Most certainly there exist chemicals or compounds that are not well-known in the art as inhibitors of cytokine secretion that could inhibit said secretion. As set forth previously essentially any toxin, e.g., bleach or benzene, would meet the limitation, yet not be considered an inhibitor of cytokine secretion. Previously Applicant argued that only BFA and monensin should be considered as such. Now Applicant appears to have replaced that argument in favor of an argument that essentially says, "if a compound/composition works in the method, it is encompassed by the method". This line of reasoning seems to be inconsistent with Applicant's previous position.

Applicant indicates in a footnote that the Examiner's question (set forth above) is improper.

It remains the Examiner's position that adequately describing a representative number of the inhibitors of cytokine secretion (just one, BFA, is disclosed) encompassed by the claims is required. Applicant does appear to confirm (at page 13 of the remarks) the Examiner's belief that Applicant does intend that the claims encompass the use of any as yet undescribed compound

or composition that may be established to function as an inhibitor of cytokine secretion in the future.

Applicant argues, "The rejection is improper because it ignores the standpoint of one of skill in the art. It is well established that in considering the sufficiency of the written description, the specification and claims are reviewed from the standpoint of one of skill in the art at the time of filing ... Within this art, inhibitors of cytokine secretion useful specifically in T cell detection methods were known at the time of the invention, and known to comprise two compounds, Brefeldin-A and monensin."

First note, Applicant appears to be reiterating an argument set forth previously, but since apparently withdrawn, that only the use of BFA and monensin would be encompassed by the claimed method. Regardless, regarding what the skilled artisan would have known or believed at the time of the invention - the skilled artisan would have believed that the method of the instant claims *would not work*. See for example the 1.132 declaration of Dr. John Altman submitted by Applicant (4/25/02) in which a competitor of the instant Inventors states that the "nothing in my own experience, and nothing certainly in the references cited by the patent Examiner, would have intimated that such an approach would be attended by a reasonable expectation of success. Indeed, much of the art taught away from the present invention, rendering the results all the more surprising." Note that said declaration was a major factor in the Examiner's decision to withdraw the previous rejection under 35 U.S.C. 103(a). Accordingly, Applicant cannot now convincingly argue what Applicant thinks "one of skill in the art" would have known simply to suit Applicant's instant needs; that matter at least has been settled. One of skill in the art would have known essentially nothing about the method of the instant claims, nor how any of its components (including inhibitors of cytokine secretion) would have functioned in said method.

5. Claims 19-24, 26-33, 35-55, 61-63, and newly added Claims 64-65 stand/are rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is not enabling. Elements critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure, for the reasons of record. As set forth in the paper mailed 12/02/02:

"At page 4, the specification discloses, "At its simplest, the methodology involves a step process, which involves culturing with the

antigen specific stimulus and analyzing an aliquot of the cultured sample for expression of one or more intracellular cytokines and/or early activation antigens in combination with one or more T-cell markers." Clearly then, *at its simplest*, the specification discloses that the claimed method requires *in vitro* antigen stimulation and culture; note that the culture step is not a claimed limitation. Further note that it is well-established that antigen stimulation in the absence of costimulation will result in anergy (not activation), thus costimulation (as recited in Claim 20) must comprise a limitation of independent Claim 19. Example 4 discloses additional required steps. For example, it is disclosed that a maximal response depended critically on the method being performed in slant tubes due to the geometry of the T cell/accessory cell interaction. The Example also discloses that the detection method of the instant claims also depended on "the inclusion of CD69 (not just any activation marker) assessment in the multiparameter protocol." Additionally, the Example discloses that the analysis "requires" the collection of at least 50,000 events. Most importantly, the specification and the post-filing art disclose/teach that the inclusion of an inhibitor of cytokine secretion is essential to the success of the claimed assay. Note that the inhibitor of cytokine secretion, BFA is used in all of the examples in the specification. Further note that, while BFA and monensin might be considered related, post-filing teachings indicate that in assays similar to those encompassed by the instant claims, the effects of the inhibitors are not identical, and the inhibitors should not be considered interchangeable. See for example, O'Neill-Andersen et al. wherein functional differences between monensin and BFA are examined. Note that the reference teaches, "A key aspect of intracellular cytokine detection is trapping the cytokine within the cell," and "We conclude that the choice of a protein transport inhibitor is an important variable in this assay." Thus, it would appear that these investigators did not find inhibitors of cytokine release to be "auxiliary to the invention" (as argued by Applicant), nor did they find it "unimportant which inhibitor is used to inhibit cytokine secretion, so long as cytokine secretion is inhibited," (also argued by Applicant)."

Applicant's arguments, filed 2/17/04, have been fully considered but they are not persuasive. Applicant argues again that Example 4 comprises only a preferred embodiment of the claimed method, ""not intended to be illustrative of all embodiments." Applicants chose to describe Example 4 as describing preferred embodiments; it is improper for Examiner to ignore the clear teaching of the specification. Features that are merely preferred are not critical."

It remains the Examiner's position that Example 4 is not just a preferred embodiment - it is the *only* embodiment of the claimed invention actually disclosed in the specification. As

set forth previously, once Applicant has disclosed a step or parameter as required or critical, said step or parameter cannot be ignored by the Examiner.

Regarding the use of slant tubes in the claimed method, Applicant argues that the specification discloses only that they were "critical" in "maximizing the responses" and comprised only a preferred embodiment.

It remains the Examiner's position that the claimed method comprises the stretching of cytokine detection well beyond the known limits of sensitivity at the time of the invention. Thus, it remains the Examiner's interpretation of the specification that steps disclosed in the only example as "critical" to "maximize" the invention are indeed required and must be claimed.

Regarding the timing of BFA inclusion in the claimed method, it has never been the Examiner's position that said timing comprised a critical element because the specification does not disclose it as such.

Regarding the inclusion of CD69 assessment in the claimed method, as the specification discloses that said assessment merely enhances detection, said assessment is not considered to be required or critical to the claimed method.

Regarding the required measurement of at least 50,000 events, Applicant argues that Example 3 "describes analyses carried out using only 48,000 events. [Thus, the] Examiner erred by ignoring the teaching in the specification that clearly shows that the analysis of 50,000 events is not a critical feature."

A review of Example 3 discloses that the "example" comprises no data and merely indicates that up to 6 parameters may be analyzed. The "example" does however disclose that 50,000 events are typically acquired of which some 48,000 remain after "fine-tuning". While it is unclear what this teaching actually means, it does not appear to be in conflict with the disclosure of Example 4 wherein the disclosure unambiguously states "accurate assessment of these responses required the routine collection and analysis of at least 50,000 events per determination."

Applicant argues that post-filing art of record (Suni et al., 1998) "provides factual evidence that refutes that assertion that elements discussed in Example 4 are critical elements without which the invention would be wholly inoperative."

Applicant is advised that it is well-established that the specification must enable the invention at the time of filing. See for example *Kawai v. Metlesics*, 480 F.2d 880, 178 USPQ 158 (CCPA 1973) wherein it states that the invention is that which is disclosed in the specification at the time of filing, and the *specification* itself must provide the invention's enablement. Thus, Applicant is not free to employ post-filing data to fine-tune or hone the claimed invention as the results of further experimentation become available.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321c may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-24, 26-33, 35-55, 61-63, and newly added Claims 64-66 stand/are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-37 and 39-40 of copending Application No. 09/526,253. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims drawn to a method of detecting antigen-specific lymphocytes comprising flow cytometrically detecting a cytokine and a T cell subset in the presence of a protein synthesis inhibitor. Note that at the time of the restriction of the '702 application the claims of said application were drawn to a method of detecting antigen-specific cytokine production. Subsequent amendment of the claims of the '702 application has necessitated this rejection. Further note that the claims of the '702 application are drawn to "an MHC-dependent nominal antigen" while the claims of the '253

application are drawn to a "vaccine antigen". However, neither antigen is defined in the specifications and said antigens are not considered to be patentably distinct. Other dependent claims of both applications recite various combinations of costimulation antigens, cytokines, and accessory molecules such as chelators and fluorophores.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant indicates that the issue will be addressed upon the finding of allowable subject matter in the '253 application.

7. No claim is allowed. Claim 66 would be allowable if recited in independent form.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

10. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact

the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

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4/24/04
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